WHAT IS CLAIMED IS:

1.   A method of identifying a tumor as responsive to treatment with an anti-HER2 antibody comprising:

a)   detecting the presence of a HER2/HER3 and/or HER2/HER1 protein complex in a sample of said tumor;

c)   identifying a tumor as responsive to treatment with anti-HER2 antibody when a complex is detected.

2.   The method of claim 1 wherein the anti-HER2 antibody blocks ligand activation of an ErbB heterodimer comprising HER2.

3.   The method of claim 1 wherein the anti-HER2 antibody is monoclonal antibody 2C4.

4.   The method of claim 1 wherein the anti-HER2 antibody is rhuMAb 2C4.

5.   The method of claim 1 wherein the presence of a HER2/HER3 and/or HER2/HER1 protein complex is detected by:

a)   immunoprecipitating any protein complexes that comprise HER2 with an anti-HER2 antibody;

b)   contacting the immunoprecipitated complexes with an antibody selected from the group consisting of anti-HER3 antibodies and anti-HER1 antibodies; and

c)   determining if an anti-HER3 and/or anti-HER1 antibody binds to the immunoprecipitated complexes,

wherein a HER2/HER3 and/or HER2/HER1 complex is detected if it is determined that anti-HER3 and/or anti-HER1 antibodies bind to the immunoprecipitated complexes.

6.　　The method of claim 1 wherein the presence of a HER2/HER3 and/or HER2/HER1 protein complex is detected by:

　　a)　　contacting the tumor sample with an anti-HER2 antibody that comprises a fluorophore;

　　b)　　contacting the tumor sample with an antibody selected from the group consisting of anti-HER3 and anti-HER1 antibodies, wherein said antibody comprises a second fluorophore;

　　c)　　determining if the first fluorophore and the second fluorophore are in close proximity by measuring the fluorescence resonance energy transfer,

　　wherein the presence of a HER2/HER3 and/or HER2/HER1 protein complex is detected if the first and second fluorophore are determined to be in close proximity.

7.　　The method of claim 1 wherein the presence of a HER2/HER3 and/or HER2/HER1 protein complex is detected by:

　　a)　　contacting the tumor sample with a first binding compound, wherein said first binding compound comprises a first target binding moiety that specifically binds HER2 and further comprises a detectable moiety linked to the first target binding moiety by a cleavable linker;

　　b)　　contacting the tumor sample with a second binding compound, wherein the second binding compound comprises a second target binding moiety that specifically binds HER3 or HER1 and an activatable cleaving agent;

　　c)　　activating the cleaving agent such that if the first binding compound and the second binding compound are in close proximity the second binding compound cleaves the cleavable linker in the first binding compound to produce a free detectable moiety; and

　　d)　　identifying the presence of the free detectable moiety,

　　wherein the presence of a HER2/HER3 or HER2/HER1 protein complex is detected when free detectable moiety is identified.

8.   The method of claim 7 wherein the first target binding moiety comprises an anti-HER2 antibody or antibody fragment.

9.   The method of claim 7 wherein the first target binding moiety comprises a HER2 receptor ligand.

10.   The method of claim 7 wherein the second target binding moiety comprises an anti-HER3 antibody or antibody fragment.

11.   The method of claim 7 wherein the second target binding moiety comprises a HER3 receptor ligand.

12.   The method of claim 7 wherein the second target binding moiety comprises an anti-HER1 antibody or antibody fragment.

13.   The method of claim 7 wherein the second target binding moiety comprises a HER1 receptor ligand.

14.   The method of claim 7 wherein the sample is obtained from a patient suffering from the tumor.

15.   The method of claim 14 wherein the sample is obtained by a biopsy of the tumor.

16.   The method of claim 14 wherein the sample is obtained by purifying circulating tumor cells from the patient's blood.

17.   The method of claim 14 wherein the sample is obtained during surgery to remove the tumor from the patient.

18.   The method of claim 1 wherein the sample of the tumor is obtained from a mouse.

19.   The method of claim 18 wherein the tumor is a xenografted tumor.

20. The method of claim 19 wherein the xenografted tumor is produced by transplanting a fragment of a human tumor into a mouse.

21. The method of claim 1 wherein the tumor is a lung tumor.

22. The method of claim 1 wherein the tumor is a mammary tumor.

23. A method for identifying tumor cells as responsive to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family comprising:

(a) providing a biological sample comprising HER2-positive tumor cells; and

(b) detecting the phosphorylation of an ErbB receptor in said biological sample, wherein said phosphorylation indicates that said tumor cells are responsive to treatment with said antibody.

24. The method of claim 23 wherein the phosphorylation of an ErbB2 (HER2) receptor is detected.

25. The method of claim 23 wherein the other member is selected from the group consisting of HER3, HER1 and HER4.

26. The method of claim 23 wherein the antibody binds HER2.

27. The method of claim 26 wherein the anti-HER2 antibody blocks ligand activation of an ErbB heterodimer comprising HER2.

28. The method of claim 27 wherein the antibody is rhuMAb 2C4.

29. The method of claim 25 wherein the antibody binds HER3.

30. The method of claim 25 wherein the antibody binds HER1.

31. The method of claim 25 wherein the antibody binds HER4.

32.   The method of claim 23 additionally comprising detecting the presence of at least one protein complex selected from the group consisting of HER2/HER3, HER2/HER1, and HER2/HER4 in the sample.

33.   The method of claim 32 wherein the presence of said protein complex or complexes is detected by:

    a)   immunoprecipitating any protein complex that comprises HER2 with an anti-HER2 antibody;

    b)   contacting the immunoprecipitated complex with at least one antibody selected from the group consisting of anti-HER3, anti-HER1, and anti-HER4 antibodies; and

    c)   determining if said anti-HER3 and/or anti-HER1 and/or anti-HER4 antibody binds to the immunoprecipitated complex,

    wherein a HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 complex is detected if it is determined that anti-HER3 and/or anti-HER1 and/or anti-HER4 antibodies bind to the immunoprecipitated complex.

34.   The method of claim 32 wherein the presence of said protein complex or complexes is detected by:

    a)   contacting the tumor sample with an anti-HER2 antibody that comprises a fluorophore;

    b)   contacting the tumor sample with an antibody selected from the group consisting of anti-HER3, anti-HER1 and anti-HER4 antibodies, wherein said antibody comprises a second fluorophore;

    c)   determining if the first fluorophore and the second fluorophore are in close proximity by measuring the fluorescence resonance energy transfer,

    wherein the presence of a HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 protein complex is detected if the first and second fluorophore are determined to be in close proximity.

35. The method of claim 32 wherein the presence of said protein complex or complexes is detected by:

a) contacting the tumor sample with a first binding compound, wherein said first binding compound comprises a first target binding moiety that specifically binds HER2 and further comprises a detectable moiety linked to the first target binding moiety by a cleavable linker;

b) contacting the tumor sample with a second binding compound, wherein the second binding compound comprises a second target binding moiety that specifically binds HER3 or HER1 or HER4 and an activatable cleaving agent;

c) activating the cleaving agent such that if the first binding compound and the second binding compound are in close proximity the second binding compound cleaves the cleavable linker in the first binding compound to produce a free detectable moiety; and

d) identifying the presence of the free detectable moiety, wherein the presence of a HER2/HER3 or HER2/HER1 or HER2/HER4 protein complex is detected when free detectable moiety is identified.

36. The method of claim 35 wherein the first target binding moiety comprises an anti-HER2 antibody or antibody fragment, or a HER2 receptor ligand.

37. The method of claim 35 wherein the second target binding moiety comprises an anti-HER3 antibody or antibody fragment, or a HER3 receptor ligand.

38. The method of claim 35 wherein the second target binding moiety comprises an anti-HER1 antibody or antibody fragment, or a HER1 receptor ligand.

39. The method of claim 35 wherein the second target binding moiety comprises an anti-HER4 antibody or antibody fragment, or a HER4 receptor ligand.

40. The method of claim 23 wherein the biological sample is tissue obtained from a tumor biopsy.

41. The method of claim 23 wherein the biological sample is a biological fluid comprising circulating tumor cells and/or circulating plasma proteins.

42. The method of claim 23 wherein the tumor is selected from the group consisting of breast cancer, prostate cancer, lung cancer, colorectal cancer and ovarian cancer.

43. The method of claim 23 wherein ErbB receptor phosphorylation is determined by immunoprecipitation of the ErbB receptor and Western blot analysis.

44. The method of claim 43 wherein ErbB receptor phosphorylation is indicated by the presence of a phospho-ErbB receptor band on the gel.

45. The method of claim 43 further comprising the step of confirming ErbB receptor phosphorylation by immunohistochemistry using a phospho-specific anti-ErbB receptor antibody.

46. The method of claim 23 wherein ErbB receptor phosphorylation is determined by immunohistochemistry.

47. A method for predicting the response of a subject diagnosed with a HER2-positive tumor to treatment with an antibody inhibiting the association of HER2 with another member of the ErbB receptor family comprising:

(a) providing a biological sample obtained from said subject, comprising HER2-positive tumor cells; and

(b) detecting phosphorylation of an ErbB receptor in said biological sample,

wherein said phosphorylation indicates that said patient is likely to respond to treatment with said antibody.

48. The method of claim 47 wherein said ErbB receptor is ErbB2 (HER2).

49.   The method of claim 47 wherein the other member is selected from the group consisting of HER3, HER1 and HER4.

50.   The method of claim 47 wherein the antibody binds HER2.

51.   The method of claim 50 wherein the anti-HER2 antibody blocks ligand activation of an ErbB heterodimer comprising HER2.

52.   The method of claim 51 wherein the antibody is rhuMAb 2C4.

53.   The method of claim 49 wherein the antibody binds HER3.

54.   The method of claim 49 wherein the antibody binds HER1.

55.   The method of claim 49 wherein the antibody binds HER4.

56.   The method of claim 47 additionally comprising detecting the presence of at least one protein complex selected from the group consisting of HER2/HER3, HER2/HER1, and HER2/HER4 in the sample.

57.   The method of claim 56 wherein the presence of said protein complex is detected by:

a)   immunoprecipitating any protein complexes that comprise HER2 with an anti-HER2 antibody;

b)   contacting the immunoprecipitated complexes with an antibody selected from the group consisting of anti-HER3, anti-HER1, and anti-HER4 antibodies; and

c)   determining if an anti-HER3 and/or anti-HER1 and/or anti-HER4 antibody binds to the immunoprecipitated complexes,

wherein a HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 complex is detected if it is determined that anti-HER3 and/or anti-HER1 and/or anti-HER4 antibodies bind to the immunoprecipitated complexes.

58.   The method of claim 56 wherein the presence of HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 protein complex is detected by:

a)   contacting the tumor sample with an anti-HER2 antibody that comprises a fluorophore;

b)   contacting the tumor sample with an antibody selected from the group consisting of anti-HER3, anti-HER1 and anti-HER4 antibodies, wherein said antibody comprises a second fluorophore;

c)   determining if the first fluorophore and the second fluorophore are in close proximity by measuring the fluorescence resonance energy transfer,

wherein the presence of a HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 protein complex is detected if the first and second fluorophore are determined to be in close proximity.

59.   The method of claim 56 wherein the presence of HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 protein complex is detected by:

a)   contacting the tumor sample with a first binding compound, wherein said first binding compound comprises a first target binding moiety that specifically binds HER2 and further comprises a detectable moiety linked to the first target binding moiety by a cleavable linker;

b)   contacting the tumor sample with a second binding compound, wherein the second binding compound comprises a second target binding moiety that specifically binds HER3, HER1, or HER4 and an activatable cleaving agent;

c)   activating the cleaving agent such that if the first binding compound and the second binding compound are in close proximity the second binding compound cleaves the cleavable linker in the first binding compound to produce a free detectable moiety; and

d)   identifying the presence of the free detectable moiety,

wherein the presence of a HER2/HER3 or HER2/HER1 or HER2/HER4 protein complex is detected when free detectable moiety is identified.

60.   The method of claim 59 wherein the first target binding moiety comprises an anti-HER2 antibody or antibody fragment, or a HER2 receptor ligand.

61.   The method of claim 59 wherein the second target binding moiety comprises an anti-HER3 antibody or antibody fragment, or a HER3 receptor ligand.

62.   The method of claim 59 wherein the second target binding moiety comprises an anti-HER1 antibody or antibody fragment, or a HER1 receptor ligand.

63.   The method of claim 59 wherein the second target binding moiety comprises an anti-HER4 antibody or antibody fragment, or a HER4 receptor ligand.

64.   The method of claim 47 wherein the biological sample is tissue obtained from a tumor biopsy.

65.   The method of claim 47 wherein the biological sample is a biological fluid comprising circulating tumor cells and/or circulating plasma proteins.

66.   The method of claim 47 wherein the tumor is selected from the group consisting of breast cancer, prostate cancer, lung cancer, colorectal cancer and ovarian cancer.

67.   The method of claim 47 wherein ErbB receptor phosphorylation is determined by immunoprecipitation of the ErbB receptor and Western blot analysis.

68.   The method of claim 67 wherein ErbB receptor phosphorylation is indicated by the presence of a phospho-ErbB receptor band on the gel.

69.   The method of claim 67 further comprising the step of confirming ErbB receptor phosphorylation by immunohistochemistry using a phospho-specific anti-ErbB receptor antibody.

70. The method of claim 47 wherein ErbB receptor phosphorylation is determined by immunohistochemistry.

71. A method for identifying a subject responsive to treatment with an anti-HER2 antibody comprising

a) detecting phosphorylation of an ErbB receptor in circulating tumor cells of said subject, and

b) determining that said subject is likely to respond to treatment with an anti-HER2 antibody if said phosphorylation is detected.

72. The method of claim 71 wherein ErbB2 (HER2) phosphorylation is detected.

73. The method of claim 72 wherein said subject is a human.

74. The method of claim 73 further comprising treating said subject with an anti-HER2 antibody.

75. The method of claim 74 wherein said anti-HER2 antibody is rhuMAb 2C4

76. A method of treating a patient comprising administering to the patient a therapeutically effective amount of an antibody which binds HER2, wherein the patient is suffering from a tumor which has been determined to comprise HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 heterodimers.

77. The method of claim 76, wherein the antibody blocks ligand activation of an ErbB heterodimer comprising HER2.

78. The method of claim 77 wherein the antibody is monoclonal antibody 2C4.

79. The method of claim 77 wherein the antibody is rhuMAb 2C4.

80.   An article of manufacture comprising a container comprising an antibody which binds HER2 and instructions for administering the antibody to a patient suffering from a tumor wherein the tumor has been determined to comprise HER2/HER3 and/or HER2/HER1 and/or HER2/HER4 heterodimers.

81.   The article of manufacture of claim 80 wherein the antibody blocks ligand activation of an ErbB heterodimer comprising HER2.

82.   The article of manufacture of claim 81 wherein the container comprises monoclonal antibody 2C4.

83.   The article of manufacture of claim 81 wherein the container comprises rhuMAb 2C4.

84.   A method of treating a patient comprising administering to the patient a therapeutically effective amount of an antibody which binds HER2, wherein the patient is suffering from a tumor which has been determined to have a phosphorylated ErbB receptor.

85.   The method of claim 84 wherein the ErbB receptor is HER2.

86.   The method of claim 84 wherein the antibody blocks ligand activation of an ErbB heterodimer comprising HER2.

87.   The method of claim 84 wherein the antibody is monoclonal antibody 2C4.

88.   The method of claim 87 wherein the antibody is rhuMAb 2C4.